FORM PTO-1390 (REV. 2/01) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney's Docket Number: 02508.0089
Customer No.: 22,852

U.S. APPLICATION NO.: (If known, see 37CFR 1.5)
09/869712

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB00/01588	November 2, 2000	November 2, 1999

TITLE OF INVENTION: **METHOD AND DEVICE FOR PREPARING A MEDICAL FLUID**

APPLICANT(S) FOR DO/EO/US: **1) Antonio BOSETTO and 2) Francesco PAOLINI**

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed with the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A Substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154 (d)(4).
19. ☐ A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4).
20. ☒ Other items or information:
    a. ☒ Copy of cover page of International Publication No. WO 01/32237 A1 with English Abstract.
    b. ☐ Copy of Notification of Missing Requirements.

Rec'd PCT/PTO 02 JUL 2001

U.S. APPLICATION NO. (If known, see 37CFR 1.5) 09/869712	INTERNATIONAL APPLICATION NO.: PCT/IB00/01588	ATTORNEY'S DOCKET NUMBER: 02508.0089

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33 (1)-(4) **$100.00**

				CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =				$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				$	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total Claims	19	- 20 =	0	x $18.00	$
Independent Claims	3	-3 =	0	x $80.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+$270.00	$270.00
TOTAL OF THE ABOVE CALCULATIONS =					$1130.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.					$
SUBTOTAL =					$1130.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest priority date (37 CFR 1.492(f)).					$
TOTAL NATIONAL FEE =					$1130.00
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +					$
TOTAL FEES ENCLOSED =					$1130.00
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 1130.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. ______ in the amount of $ ______ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING**: Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P
1300 I Street, N.W.
Washington, D.C. 20005-3315
EFC/FPD/sci
DATED: July 2, 2001

[signature] 20,338
SIGNATURE
Ernest F. Chapman
NAME/REGISTRATION NO.

METHOD AND A DEVICE FOR PREPARING A MEDICAL LIQUID

The present invention relates to a method and a device for preparing a medical liquid.

The invention has an application in particular in the treatment of renal insufficiency, where it can be used for preparing a dialysis liquid. In this context, the invention is particularly suitable for treating patients whose internal medium presents an excess of potassium.

The kidneys perform many functions, including elimination of water, excretion of catabolites (or waste products of metabolism, such as urea and creatinine), regulation of the concentration of electrolytes in the blood (sodium, potassium, magnesium, calcium, bicarbonates, phosphates, chlorides), and regulation of the acid-base balance of the internal medium, which balance is obtained in particular through the elimination of weak acids (phosphates, monosodium acids) and through the production of ammonium salts.

In persons who have lost the use of their kidneys, since these excretory and regulatory mechanisms no longer function, the internal medium becomes charged with water and waste products of metabolism and presents an excess of electrolytes (sodium in particular), and, in general, acidosis, with the pH of the blood plasma shifting towards 7.

To remedy kidney dysfunction, the conventional practice is to treat the blood by extracorporeal circulation in a semipermeable membrane exchanger (hemodialyzer), with circulation, on either side of the membrane, of the patient's blood and of a dialysis liquid comprising the main electrolytes of the blood (chlorides, bicarbonates, sodium, calcium, potassium, magnesium) in concentrations close to those of the blood of a healthy subject. As a result of the physical phenomenon called dialysis, the molecules migrate from the liquid in which their concentration is highest to the liquid in which their concentration is lowest.

A significant electrolytic change in uremic patients is

the increase in the potassium concentration of the plasma. Now, hyperkalemia (too high a concentration of potassium) is associated with incidents linked to hyperpolarization of the membrane of the neuromuscular cells, which can result in hypokinetic arrhythmia and complete atrioventricular block. One of the objectives of dialysis treatment is therefore to eliminate the excess potassium accumulated by the patients between two treatment sessions. In accordance with the physical principle cited above, the quantity of potassium eliminated during treatment depends directly on the difference between the concentration of the potassium in the plasma and the concentration of the potassium in the dialysis liquid, which is generally fixed at a constant level, less (approximately 2 mEq/l) than the physiological level (approximately 3.5 mEq/l).

At the start of conventional dialysis treatment, a patient with hyperkalemia (whose plasma potassium concentration can be as high as 10 mEq/l) is exposed to the undesirable effects resulting from the considerable difference between the potassium concentration of his plasma and that of the dialysis liquid: this increased gradient in fact causes a substantial diffusive flow of potassium across the membrane of the hemodialyzer, which in turn causes a substantial flow of potassium across the membrane of the cells, which affects the electric potential of the membrane at rest and, consequently, the cellular excitability. As this mechanism also influences the cardiac pacemaker cells, the patent runs the risk of cardiac arrhythmia during the dialysis treatment. This phenomenon is naturally heightened in cases of cardiac weakness and can lead to a reduction in the ejection volume affecting the cardiovascular circulation.

A particular object of the invention is therefore to modify the conditions of conventional dialysis treatment, without however affecting its effectiveness, in such a way that patients with hyperkalemia are no longer exposed to the risks mentioned above.

A general object of the invention is to conceive a device and a method for preparing a treatment liquid which can be

used for extracorporeal treatment of blood, and by means of which the concentration of two ionic substances can be adjusted separately, in particular sodium and potassium (or calcium, or magnesium).

According to the invention, this object is achieved by means of a method for preparing a medical liquid from a liquid, such as water, and two concentrated solutions, comprising the following steps:

- circulating the liquid in a conduit, at a flowrate Q0;
- injecting into the conduit, at a flowrate Q1, a first concentrated solution containing a first ionic substance A and a second ionic substance B, the ionic substances A and B having, respectively, in the first concentrated solution, a concentration [Asol] and a first concentration [B1sol];
- injecting into the conduit, at a flowrate Q2, a second concentrated solution containing the first ionic substance A and the second ionic substance B, the first ionic substance A having, in the second concentrated solution, the same concentration [Asol] as in the first concentrated solution, and the second ionic substance B having, in the second concentrated solution, a second concentration [B2sol] different than the first concentration [B1sol] in the first concentrated solution;
- regulating the injection flowrate Q1 and the injection flowrate Q2 of the first and second concentrated solutions in such a way that at any given time the diluted solution resulting from the mixing of the liquid and the concentrated solutions has a desired concentration [Ades] of first substance A and a desired concentration [Bdes] of second substance B.

According to one characteristic of the invention, the injection flowrate Q1 and the injection flowrate Q2 of the concentrated solutions A and B are varied over the course of time in such a way that the concentration of the second substance B in the diluted solution varies over the course of time in accordance with a predetermined profile.

According to another characteristic of the invention, the flowrate Q0 of the liquid in the conduit is constant, and the

sum of the injection flowrates Q1 + Q2 of the concentrated solutions A and B is maintained constant in such a way that the concentration of the first substance A in the diluted solution remains substantially constant.

According to yet another characteristic of the invention, the injection flowrate Q1 and the injection flowrate Q2 of the concentrated solutions A and B are varied over the course of time in such a way that the concentration of the first substance A in the diluted solution varies over the course of time in accordance with a predetermined profile.

The invention also relates to a device for preparing a treatment liquid from a liquid, such as water, and two concentrated solutions, comprising:

- a conduit with a first end intended to be connected to a source of liquid, such as water, and a second end for delivering a treatment liquid;

- first injection means for injecting into the conduit, at a flowrate Q1, a first concentrated solution containing a first ionic substance A and a second ionic substance B, the ionic substances A and B having, respectively, in the first concentrated solution, a concentration [Asol] and a first concentration [B1sol];

- second injection means for injecting into the conduit, at a flowrate Q2, a second concentrated solution containing the first ionic substance A and the second ionic substance B, the first ionic substance A having, in the second concentrated solution, the same concentration [Asol] as in the first concentrated solution, and the second ionic substance B having, in the second concentrated solution, a second concentration [B2sol] different than the first concentration [B1sol] in the first concentrated solution;

- regulating means for regulating the first and second injection means and for adjusting the injection flowrate Q1 and the injection flowrate Q2 of the first and second concentrated solutions in such a way that at any given time the diluted solution resulting from the mixing of the liquid and the concentrated solutions has a desired concentration [Ades] of first substance A and a desired concentration [Bdes]

of second substance B.

In one embodiment of the invention, the device for preparing treatment liquid is incorporated in a hemodialysis system, the substance A is sodium and the substance B is potassium, calcium, or magnesium. As the sodium concentration in a dialysis liquid is much higher than the potassium (calcium or magnesium) concentration, the potassium concentration can be very precisely regulated by measuring the conductivity of the mixture forming in the conduit immediately downstream of the site of injection of the first concentrated solution into the conduit, and of the mixture forming in the conduit immediately downstream of the site of injection of the second concentrated solution into the conduit (there is an excellent correlation between the conductivity of a solution and its sodium concentration).

Moreover, there is no danger of influencing the plasma potassium or calcium concentration of a patient using a very dilute dialysis solution prepared and administered by a system equipped with reliable means for measuring concentrations, which would not be the case if this objective were achieved by injection of more concentrated solution.

The invention also relates to a kit of solutions for extracorporeal treatment of blood, comprising two concentrated solutions and a bag with two compartments intended to contain each of the solutions from the kit. Each of the solutions contains at least two ionic substances A and B, the ionic substance A having the same concentration in the two solutions and the ionic substance B having different concentrations in two solutions.

According to one characteristic of the invention, the two solutions are identical except for one ionic substance whose concentration differs from one solution to the other.

Other characteristics and advantages of the invention will become more apparent on reading the following description. Reference will be made to the attached drawings, in which:

Figure 1 is a diagram showing a device for treatment of blood;

Figure 2 shows a bag with two compartments for containing the two concentrated solutions from a treatment kit; and

Figure 3 is a graph showing several profiles of variation in the potassium concentration of a dialysis liquid.

The hemodialysis system shown in Figure 1 comprises a hemodialyzer 1 with two compartments 2, 3 separated by a semipermeable membrane 4. A first compartment 2 has an inlet connected to a blood withdrawal conduit 5 on which a circulation pump 6 is arranged, and an outlet connected to a blood return conduit 7 on which a bubble trap 8 is interposed.

An infusion device comprising a pump 10 and a balance 11 is provided for injecting into the bubble trap 8 the contents of a bag 9 of infusion liquid containing sodium bicarbonate. The bag 9 is suspended from the balance 11 and it is connected to the bubble trap 8 via a conduit 12 on which the infusion pump 10 is arranged. The balance 11 serves to control the pump 10 so that the flowrate of the infusion liquid is equal to a reference flowrate.

The second compartment 3 of the hemodialyzer 1 has an inlet connected to a conduit 12 for supply of fresh dialysis liquid, and an outlet connected to a conduit 13 for removal of spent liquid (dialysis liquid and ultrafiltrate).

The supply conduit 12 connects the hemodialyzer 1 to a device 14 for preparing dialysis liquid, comprising a main conduit 15 whose upstream end is intended to be connected to a source of running water. First and second subsidiary channels 16, 17 are connected to this main conduit 15.

According to the invention, the free end of the first subsidiary conduit 16 is intended to be immersed in a container 18 for a first concentrated saline solution containing sodium chloride, calcium chloride, magnesium chloride and potassium chloride. This first conduit 16 is equipped with a pump 19 for metering the first concentrated solution into the dialysis liquid, which is controlled as a function of the comparison between 1) a first reference value of conductivity for the solution forming at the junction of the main conduit 15 and the first subsidiary conduit 16, and 2) the value of the conductivity of this solution measured by

means of a first conductivity probe 20 arranged on the main conduit 15 immediately downstream of the junction between the main conduit 15 and the first subsidiary conduit 16.

According to the invention, the free end of the second subsidiary conduit 17 is intended to be immersed in a container 21 for a second concentrated saline solution containing sodium chloride, calcium chloride, magnesium chloride and potassium chloride. This second solution contains the same ionic substances as the first solution and in the same concentrations, except for potassium whose concentration is different. The second conduit 17 is equipped with a pump 22 for metering the second concentrated solution into the dialysis liquid, which is controlled as a function of the comparison between 1) a second reference value of conductivity for the solution forming at the junction of the main conduit 15 and the second subsidiary conduit 17, and 2) the value of the conductivity of this solution measured by means of a second conductivity probe 23 arranged on the main conduit 15 immediately downstream of the junction between the main conduit 15 and the second subsidiary conduit 17.

The conduit 12 for supply of dialysis liquid forms the continuation of the main conduit 15 of the device 14 for preparation of dialysis liquid. Arranged on this supply conduit 12, in the direction of circulation of the liquid, are a first flowmeter 24 and a first circulation pump 25.

The downstream end of the conduit 13 for removal of spent liquid is intended to be connected to the drain. Arranged on this conduit, in the direction of circulation of the liquid, are a probe 26 for measuring the potassium concentration, a second circulation pump 27, and a second flowmeter 28. An extraction pump 29 is connected to the removal conduit 13 upstream of the second circulation pump 27.

The hemodialysis system represented in Figure 1 also comprises a calculation and control unit 30. This unit is connected to a screen 31 and to a keyboard 32 via which the user inputs various reference values: flowrate reference values (blood flowrate Qb, dialysis liquid flowrate Qd, infusion solution flowrate Qinf), reference values for

concentration of ionic substances in the dialysis liquid, reference value for the duration of treatment T, reference value for loss of weight WL. Moreover, the calculation and control unit 30 receives information emitted by the measurement elements of the system, such as the flowmeters 24, 28, the conductivity probes 20, 23, and the probe 26 for measuring potassium concentration. As a function of the instructions received and of programmed operating modes and algorithms, it controls the drive elements of the system, such as the pumps 6, 10, 19, 22, 25, 27, 29.

According to the invention, the concentration of sodium and the concentration of potassium in the dialysis liquid can be adjusted independently of one another: for a constant flowrate Q0 of water, the concentration of sodium depends on the sum of the flowrate Q1 of the first concentrated solution injected via the pump 19 into the main conduit 15 and the flowrate Q2 of the second concentrated solution injected via the pump 22 into the main conduit 15, while the concentration of potassium depends on the ratio of the flowrates Q1, Q2 of the first and second concentrated solutions. The concentration of sodium and of potassium in the dialysis liquid is chosen as a function of each individual patient. It can be set at a fixed value. According to the invention, for patients with hyperkalemia, the potassium concentration of the dialysis liquid is modified continuously during the treatment session according to a predetermined profile of variation.

Example:

The hemodialysis system described above is equipped with a bag 50 made of flexible transparent plastic, as is represented in Figure 2, and comprising two compartments 51 and 52 corresponding respectively to the containers 18 and 21 in Figure 1. The bag 50 is provided in its upper part with eyelets 53 by which it can be suspended vertically from a suitable support. Each compartment 51, 52 is equipped at its base with an access tube 54, 55 provided at its end with a connection element 56, 57 intended to cooperate with a complementary connection element fixed to the end of the subsidiary conduits 16, 17 of the device 14 for preparation of

dialysis liquid. A clip 58, 59 is arranged on each of the tubes 54, 55.

The compartment 51 (container 18) contains the following substances, in the following concentrations:

NaCl: 284.31 g/l

KCl: 19.57 g/l

CaCl2: 10.29 g/l

MgCl2: 2.63 g/l

Anhydrous glucose: 35 g/l.

The compartment 52 (container 21) contains the following substances, in the following concentrations:

NaCl: 284.31 g/l

KCl: 0 g/l

CaCl2: 10.29 g/l

MgCl2: 2.63 g/l

Anhydrous glucose: 35 g/l.

By means of these two solutions it is possible, according to the invention, to prepare a dialysis liquid having a sodium concentration of between approximately 130 mEq/l and approximately 155 mEq/l, and a potassium concentration varying, during a treatment session, from between an initial value of approximately 2.5 mEq/l and approximately 5.5 mEq/l and a final value of between approximately 1 mEq/l and approximately 2 mEq/l.

Figure 3 shows four profiles of variation of the potassium concentration of a dialysis liquid, which profiles can be obtained using the device 14 for preparation of dialysis liquid connected to the bag 50 with two compartments containing the concentrated solutions which have just been described. In this figure, the broken line shows the constant potassium concentration of a conventional dialysis liquid, that is to say 2 mEq/l.

The hemodialysis apparatus which has just been described functions in the following manner.

An operator inputs to the control unit 30, via the keyboard 32, conventional reference values corresponding to the various parameters of treatment (prescription), namely the blood flowrate Qb, the dialysis liquid flowrate Qd, the

infusion flowrate Qinf of the bicarbonate solution, the total weight loss WL (quantity of plasma water to be withdrawn from patient by ultrafiltration), the total duration T of the session, and the sodium concentration of the dialysis liquid.

According to the invention, the operator also inputs, to the control unit, an information item or a series of information items concerning the potassium concentration of the dialysis liquid, which can be either a fixed reference value or one of the variation profiles stored beforehand in the control unit, corresponding for example to one of the graphs in Figure 3. The operator can also create and store a profile appropriate to an individual client.

According to an alternative embodiment of the invention, the potassium concentration of the dialysis liquid is adjusted via the control unit 30 in the following manner: a dialysis liquid having a potassium concentration corresponding to a predetermined reference value is initially circulated in the hemodialyzer 1, and this reference value is compared with the value of the potassium concentration in the spent liquid, measured by the probe 26. The control unit 30 subsequently controls the pumps 19, 22 of the device 14 for preparation of treatment liquid in such a way that the difference between the reference value and the measured value remains substantially equal to a given value, corresponding to a difference, acceptable for the patient, between the potassium concentration of the plasma and that of the dialysis liquid.

After a kit of concentrated solutions, such as the bag described above, has been connected to the conduits 16, 17 of the device 14 for preparation of dialysis liquid, the dialysis liquid circuit is filled with dialysis liquid. To do this, the main conduit 15 is connected to a source of running water and the pumps 19, 22, 25, 27 are started up. The pumps 19 and 22 are regulated via the control unit 30 in such a way that the potassium concentration and the sodium concentration of the dialysis liquid are equal to the corresponding reference values. The pumps 25, 27 for circulating dialysis liquid are regulated via the control unit 30 in such a way that the flowrate of the pump 25 situated upstream of the hemodialyzer

1 is equal to the reference flowrate Qd (500 ml/min, for example) and so that the flowrate of the pump 27 situated downstream of the hemodialyzer 1 is such that the flowrates measured by the flowmeters 24, 28 are equal.

At the same time as the dialysis liquid circuit is filling with the dialysis liquid according to the prescription, the circuit for extracorporeal blood circulation is rinsed and filled with sterile physiological liquid.

When priming of the dialysis liquid circuit and of the blood circuit is completed, the blood circuit is connected to the patient and the treatment proper can commence: the pumps 19, 22 of the device 14 for preparation of dialysis liquid, and the pumps 25, 27 for circulating the dialysis liquid, continue functioning, while the blood pump 6, the extraction pump 29 and the infusion pump 10 are started up. The blood pump 6 is set at the reference flowrate Qb (for example 200 ml/mn), the infusion pump 10 is set at the reference flowrate Qinf, and the extraction pump 29 is set at a flowrate QUF calculated by the control unit 30 on the basis of the reference values for total weight loss WL, infusion flowrate Qinf and total duration of treatment T.

The invention which has just been described is open to variants.

In the same way as the potassium concentation, the calcium or magnesium concentration can be adjusted to the needs of each individual patient.

With the preparation device according to the invention, it is possible to simultaneously adjust the potassium concentration of a dialysis liquid according to a first defined variation profile and the sodium concentration of the same dialysis liquid according to a second defined variation profile.

A probe for measuring the potassium concentration can be mounted on the supply conduit 12 in order to provide a measured value of the potassium concentration which will be used, for example, to calculate the difference between this value and the value measured downstream of the hemodialyzer 1 by the probe 26.

CLAIMS

1. Method for preparing a medical liquid from a liquid, such as water, and two concentrated solutions, comprising the following steps:

- circulating the liquid in a conduit (15), at a flowrate Q0;

- injecting into the conduit (15), at a flowrate Q1, a first concentrated solution containing a first ionic substance A and a second ionic substance B, the ionic substances A and B having, respectively, in the first concentrated solution, a concentration [Asol] and a first concentration [B1sol];

- injecting into the conduit (15), at a flowrate Q2, a second concentrated solution containing the first ionic substance A and the second ionic substance B, the first ionic substance A having, in the second concentrated solution, the same concentration [Asol] as in the first concentrated solution, and the second ionic substance B having, in the second concentrated solution, a second concentration [B2sol] different than the first concentration [B1sol] in the first concentrated solution;

- regulating the injection flowrate Q1 and the injection flowrate Q2 of the first and second concentrated solutions in such a way that at any given time the diluted solution resulting from the mixing of the liquid and the concentrated solutions has a desired concentration [Ades] of first substance A and a desired concentration [Bdes] of second substance B.

2. Method according to Claim 1, characterized in that it consists in varying over the course of time the injection flowrate Q1 and the injection flowrate Q2 of the concentrated solutions A and B in such a way that the concentration of the second substance B in the diluted solution varies over the course of time in accordance with a predetermined profile.

3. Method according to Claim 2, characterized in that the flowrate Q0 of the liquid in the conduit is constant, and in that the sum of the injection flowrates Q1 + Q2 of the concentrated solutions A and B is maintained constant in such a way that the concentration of the first substance A in the diluted solution remains substantially constant.

4. Method according to one of Claims 1 to 3, characterized in that it consists in varying over the course of time the injection flowrate Q1 and the injection flowrate Q2 of the concentrated solutions A and B in such a way that the concentration of the first substance A in the diluted solution varies over the course of time in accordance with a predetermined profile.

5. Device for preparing a treatment liquid from a liquid, such as water, and two concentrated solutions, comprising:

- a conduit (15) with a first end intended to be connected to a source of liquid, such as water, and a second end for delivering a treatment liquid;

- first injection means (19) for injecting into the conduit (15), at a flowrate Q1, a first concentrated solution containing a first ionic substance A and a second ionic substance B, the ionic substances A and B having, respectively, in the first concentrated solution, a concentration [Asol] and a first concentration [B1sol];

- second injection means (22) for injecting into the conduit (15), at a flowrate Q2, a second concentrated solution containing the first ionic substance A and the second ionic substance B, the first ionic substance A having, in the second concentrated solution, the same concentration [Asol] as in the first concentrated solution, and the second ionic substance B having, in the second concentrated solution, a second concentration [B2sol] different than the first concentration [B1sol] in the first concentrated solution;

- regulating means (20, 23, 30) for regulating the first and second injection means (19, 22) and for adjusting the injection flowrate Q1 and the injection flowrate Q2 of the

first and second concentrated solutions in such a way that at any given time the diluted solution resulting from the mixing of the liquid and the concentrated solutions has a desired concentration [Ades] of first substance A and a desired concentration [Bdes] of second substance B.

6. Device according to Claim 5, characterized in that the regulating means (20, 23, 30) are provided for varying over the course of time the injection flowrate Q1 and the injection flowrate Q2 of the concentrated solutions A and B in such a way that the concentration of the second substance B in the diluted solution varies over the course of time in accordance with a predetermined profile.

7. Device according to either of Claims 5 and 6, characterized in that the regulating means (20, 23, 30) are provided for varying over the course of time the injection flowrate Q1 and the injection flowrate Q2 of the concentrated solutions A and B in such a way that the concentration of the first substance A in the diluted solution varies over the course of time in accordance with a predetermined profile.

8. Device according to Claim 6, characterized in that the regulating means (20, 23, 30) are provided for maintaining constant the sum of the injection flowrates Q1 + Q2 of the concentrated solutions A and B, in such a way that, for a constant flowrate Q0 of the liquid in the conduit, the concentration of the first substance A in the diluted solution remains substantially constant.

9. Device according to one of Claims 1 to 8, characterized in that the substance A is sodium, and in that the substance B is potassium, calcium, or magnesium.

10. Device according to Claims 6 and 9, characterized in that the substance B is potassium, and in that the predetermined concentration profile is a descending profile whose initial value is between approximately 2.5 mEq/l and approximately 5.5

mEq/l and whose final value is between approximately 1 mEq/l and approximately 2 mEq/l.

11. System for extracorporeal treatment of blood comprising:

- a device for preparing treatment liquid according to one of Claims 5 to 10;
- a conduit (12) for supply of treatment liquid, for connecting the conduit (15) of the treatment device to an inlet of a membrane exchanger (1);
- a conduit (13) for removing spent liquid, intended to be connected to an outlet of the membrane exchanger (1);
- a first device for measuring the concentration of the ionic substance B in the treatment liquid, arranged on the preparation conduit;
- a second device for measuring the concentration of the ionic substance B in the spent liquid, arranged on the removal conduit.

12. Treatment system according to Claim 11, characterized in that the regulating means (20, 23, 30) are provided for regulating the first and second injection means (19, 22) on the basis of the information supplied by the first and second devices for measuring the concentration of the ionic substance B.

13. Treatment system according to either of Claims 11 and 12, characterized in that it additionally comprises means (10, 11, 12) for infusing a patient with a third solution containing at least one ionic substance C absent from the treatment liquid.

14. Preparation device according to Claim 13, characterized in that the substance C is bicarbonate.

15. Kit of solutions for extracorporeal treatment of blood, comprising two concentrated solutions containing at least two ionic substances A and B, the ionic substance A having the same concentration in the two solutions and the ionic substance B having different concentrations in the two

solutions.

16. Kit of solutions according to Claim 15, characterized in that it comprises two solutions which are identical except for one ionic substance whose concentration differs from one solution to the other.

17. Bag (50) with two compartments (51, 52) for containing each of the solutions from the kit according to Claims 15 and 16.

ABSTRACT

A method for preparing a medical liquid from a liquid, such as water, and two concentrated solutions comprises the following steps:

- circulating the liquid in a conduit (15), at a flowrate Q0;

- injecting into the conduit (15), at a flowrate Q1, a first concentrated solution containing a first ionic substance A and a second ionic substance B, the ionic substances A and B having, respectively, in the first concentrated solution, a concentration [Asol] and a first concentration [B1sol];

- injecting into the conduit (15), at a flowrate Q2, a second concentrated solution containing the first ionic substance A and the second ionic substance B, the first ionic substance A having, in the second concentrated solution, the same concentration [Asol] as in the first concentrated solution, and the second ionic substance B having, in the second concentrated solution, a second concentration [B2sol] different than the first concentration [B1sol] in the first concentrated solution;

- regulating the injection flowrate Q1 and the injection flowrate Q2 of the first and second concentrated solutions in such a way that at any given time the diluted solution resulting from the mixing of the liquid and the concentrated solutions has a desired concentration [Ades] of first substance A and a desired concentration [Bdes] of second substance B.

Fig. 1

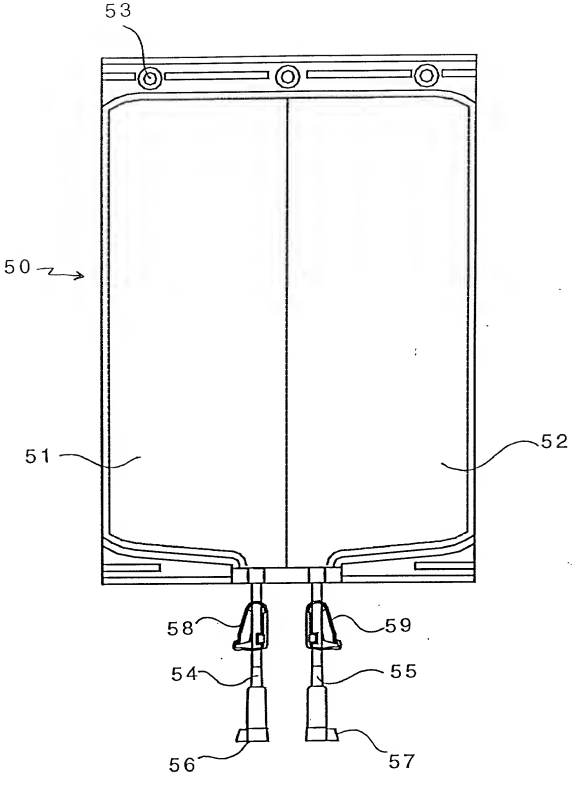

Fig. 2

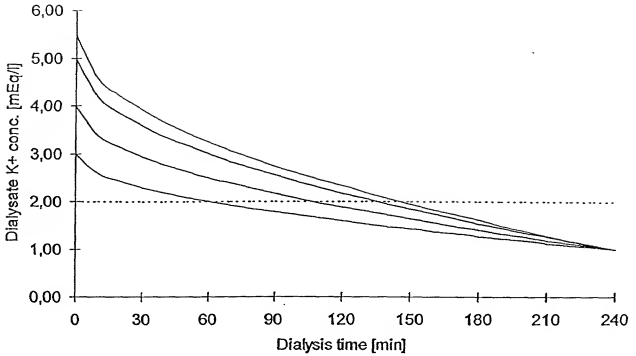
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Dialysate K+ conc. [mEq/l]
0
30
60
90
120
150
180
210
240
Dialysis time [min]

Fig.3

Attorney Docket No. 02508.0089

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: METHOD AND DEVICE FOR PREPARING A MEDICAL FLUID the specification of which ☐ is attached and/or ☐ was filed on July 2, 2001 as United States Application Serial No. 09/869,712 or PCT International Application No. PCT/IB00/01588 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C.
ITALY	T099A000948	November 2, 1999	☒ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 29,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,025; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; and David A. Manspeizer, Reg. No. 37,540 and _____. Please address all correspondence to FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. 1300 I Street, N.W., Washington, D.C. 20005, Telephone No. (202) 408-4000.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full Name of First Inventor	Inventor's Signature	Date
Antonio BOSETTO		31 MAY 01
Residence: Via Ippolito Nievo 18/A, I-41036 Mirandola Italy		Citizenship: Italy
Post Office Address: Via Ippolito Nievo 18/A, I-41036 Mirandola Italy		

Listing of Inventors Continued on Page 2 hereof. ☒ Yes ☐ No

Listing of Inventors Continued From Page 1 hereof.

Attorney Docket No. 02508.0089

Full Name of Second Inventor Francesco PAOLINI	Inventor's Signature	Date 28/08/2000
Residence Strada Forghieri, 229, Ganaceto, I-41010 Modena Italy		Citizenship Italy
Post Office Address Strada Forghieri, 229, Ganaceto, I-41010 Modena Italy		
Full Name of Third Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Fourth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Fifth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Sixth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Seventh Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Eighth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Ninth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		

Listing of Inventors Continued on Page 2 hereof. ☐ Yes ☐ No